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Applicant:	Bamborough, et al.	19 May 2010
Serial No.:	10/587,790	Group Art Unit: 1614
Filed:	28 July 2006	Examiner: A. Pagonakis
Title:	FUSED HETEROARYL DERIVATIVES FOR USE AS P38 KINASE INHIBITORS	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF UNDER 37 CFR § 41.37

Sir:

This brief is in furtherance of Applicants Notice of Appeal, filed in this case on 19 October 2009.

The fee of \$540.00 for filing this Appeal Brief is supplied herewith as well as the fee of \$2350 for a five month extension of time. The Director is hereby authorized to charge any deficiency in the fee due with the filing of this paper, or credit any overpayment, to our Deposit Account, No. 19-2570.

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I. Real Party in Interest

The real party in interest is Applicants' assignee:

SmithKline Beecham Corporation, located at One Franklin Plaza, P.O. Box 7929,
Philadelphia, PA 19101, USA.

II. Related Appeals and Interferences

There are no related appeals or interferences which will directly affect, or be directly affected by, or have a bearing on the Board's Decision in this Appeal.

III. Status Of Claims

Claims 1-13, and 19-22 are pending. Claims 18 and 23 are withdrawn from consideration in the application. Claims 1-13, and 19-2 (all pending claims) are rejected and are the subject of this appeal. The status of the claims is as follows:

Claims 1-13	Rejected
Claims 14-17	Cancelled.
Claim 18	Withdrawn.
Claims 19-22	Rejected.
Claim 23	Withdrawn

IV. Status Of Amendments

There were no amendments to the claims filed in Applicants Response of 19 October 2009 to the Examiner's Final Office Action rejecting Claims 1 to 13 and 19 to 22 of 15 July 2009. The Examiner's Advisory Action of 29 October 2009 entered Applicants comments into the record. Therefore, the claims on appeal are Claims 1 to 13, and 19 to 22, and the attached Appendix of Claims is believed to be an accurate listing of the claims.

There are no outstanding amendments at the present time.

V. Summary of Claimed Subject Matter

There is one (1) independent claim under appeal, Claim 1.

Independent Claim 1 is directed to compounds of Formula (I), or a pharmaceutically acceptable salt thereof¹. Claims 2 -11 are dependent claims directed to various substituent groups contained within the Formula (I) genus². Claim 12 is directed to various species or salts thereof. Claim 13 is a pharmaceutical composition comprising a compound of Formula (I), or pharmaceutically acceptable salt thereof, dependent upon Claim 1.

Withdrawn claim 18 is an originally filed process claim to yield a compound of Formula (I), or pharmaceutically acceptable salt thereof, dependent upon Claim 1.

Claims 19-21 are dependent claims directed to the various substituent groups, dependent upon Claim 2.³

Claim 22 is a pharmaceutical composition claim dependent upon the original species claim, claim 12.

Withdrawn Claim 23 is directed to species claims (or salts thereof) contained in the Formula (I). Claim 23 was added in Applicants response to the Restriction Requirement on 23 October 2008.⁴

There are no methods of use claims presently pending in the application.

¹ Page 1, lines 7-32, page 2, lines 1 to 29.

² Claims 2-13 are as originally filed; also see specification, Page 1, lines 7-32, through 10, line 15.

³ Claims 19-21 parallel original filed claims but dependent upon claim 2. Claims 19-22 were added in the preliminary amendment of 28 July 2006.

⁴ Claim 23 encompasses the cancelled species of original Claim 11.

VI. Ground Of Rejection To Be Reviewed on Appeal

There is one ground of rejection in the application.

Claims 1 to 13 and 19 to 22 are rejected under 35 USC §112, 1st paragraph as failing to comply with the enablement requirement.

It is believed that the rejection to the claims as stated in the Office Action of 7 January 2009 is that the specification while being “enabling for making the compounds of formula I, does not reasonably provide enablement for use of the same. The Specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims”. (Page 3, last ¶, Office Action). Applicant’s arguments of 29 October 2009 and this Appeal Brief are based upon this understanding.

VII. Arguments

The Examiner has erred in rejecting the claims as nonenabling under the provisions of 35 U.S.C. §112, first paragraph. Applicants request reversal of the outstanding rejection for the reasons set forth herein.

THE INVENTION

Briefly, the Applicant's invention relates to novel compounds of Formula (I), and pharmaceutically acceptable salts thereof, along with their pharmaceutical compositions, and method of treating a p38 kinase mediated disease with a compound of Formula (I).

Compounds of Formula (I) are stated to possess activity as a p38 kinase inhibitors⁵.

There is a legal requirement that the compounds possess at least one credible utility. At the time of filing of this application, the area of p38 mediated diseases for which inhibition of the kinase would be useful was both well known and art recognized. The p38 kinase had been identified and isolated in the early 90's and many companies have filed patent applications on different pharmacophores with varying disease states linked to inhibition of this enzyme. Applicants have provided in their various Information Disclosure Statements and accompanying PTO 1449 forms a wide range of supporting documentation of the linkage of p38 mediated diseases to inhibition of the kinase. Many patents have been granted by the USPTO to compounds having this same utility. In Applicants response of 19 October 2009, it was noted that from the US government's clinical trials.gov web site there were 34 clinical trials listed. Consequently, Applicants believe that they have thoroughly met the burden of enablement.

In furtherance of the enablement rejection, the Examiner cited the five (5) Wands factors which cover the nature of the invention, claim breadth, predictability or unpredictability of the art; the

⁵ Page 1, lines 1-5; page 28, lines 26-42; and page 29, lines 1-20.

amount of direction or guidance presented, the presence or absence of working examples, the quantity of experimentation necessary, the state of the prior art and the relative skill of those in the art.

The claims herein teach a genus of compounds that have utility as inhibitors of the p38 kinase. The specification describes 69 chemical intermediates to make compounds of Formula (I), several general methods of making and 82 Examples of compounds encompassed by the genus of Formula (I). The Examiner does not appear to have made a rejection that the specification does not teach how to make compounds of Formula (I) and therefore no additional arguments are set forth herein with respect thereto.

With respect to the requirement of “how to use” the compounds of Formula (I), the specification clearly contains sufficient information on how to formulate a composition using a compound of Formula (I), see pages 22, lines 1 to 42 through page 32, lines 1 -11. More specifically, page 26, lines 15-17, page 27, lines 11-14; and page 28, lines 1 to 9 on dosage amounts.

As to utility, see pages 107, lines 35 to 41 through pages 110, lines 1 – 23 which clearly teach suitable assays to determine activity of the compounds as a p38 kinase inhibitor. On page 110, lines 21-22 the specification teaches that:

“The compounds described in the Examples were tested in at least one of the assays described above and had either IC₅₀ values of <10 μ M or pK_i values of >6.”

The Examiner comments that:

“ the assay simply leads to the conclusion that binding in fact occurs. The assay does not lead the conclusion that this binding is null, inhibitory or activating. Secondly, Applicants alleges that the assay is a well recognized assay for determine p 38 kinase activity but advances no specific evidence aside from Counsel’s own argument in support of this position.” See Office Action of 15 July 2009 (page 8, first ¶).

:

It should first be noted, of course, that here is no actual requirement to provide data in the specification. It should also be noted that throughout the instant specification the aim is to “inhibit” the p38 kinase.⁶ More specifically the compounds are useful in the treatment of a condition or disease state mediated by p38 kinase activity or mediated by cytokines produced by p38 kinase activity.

The binding assay clearly teaches “inhibition” of the kinase⁷. Consequently the Examiner’s argument that one cannot be lead to the conclusion that this assay is “null, inhibitory or activating” is simply a non-sequitor. The Examiner has failed to read the assay. It also appears that the Examiner has failed to understand the linkage of inhibition of the p38 kinase to reduction of anti-inflammatory cytokines, consequently leading to a reduction in the inflammation associated with a disease or disease state mediated by p38 kinase, as evidenced by the many articles submitted in during prosecution. Therefore, Applicants believe that as the specification teaches that the 82 Examples were all active in an assay that teaches the skilled artisan if a compound has activity, not only has claim breadth been demonstrated so has enablement.

With respect to the State of the Art, Applicant’s are not only the first to find and isolate the various isoforms of the p38 Kinase, they are the holder of a number of US Granted patents thereon, see for instance US 5,783,664; US 5,871,934; US 5,955,366; US 5,777,097; and US 6,361,773. The described Fluorescence Anisotropy Kinase Binding Assay is simply the most current assay used by the Applicants at the time of filing of this application. An earlier kinase assay, entitled “CSBP/p38 Kinase Assay” also has appeared in many of Applicants granted patents, for instance, see US 7,323,472; US 7,235,551 and US 7,700,768. Clearly, these assays all teach positive inhibitory activity in the binding assays, whether it be an IC₅₀ number or a pIC₅₀ number. In contrast to this application which stated the compounds had “either IC₅₀ values of <10 μM or pK_i values of >6” other applications of Applicants have stated that

⁶ Page 1, line 5; page 28, lines 16-19, and lines 27-42; page 29, lines 1-41 and page 30, lines 1-6

⁷ Page 108, lines 10-36; page 109, 110 and 111, lines 1-8

“Compounds are considered active in this assay if they demonstrate a pIC₅₀ of greater than 4.6 up to about a pIC₅₀ of 9.0”.

Later filed applications present yet another variation of the assay as a “Time-resolved fluorescence resonance energy transfer kinase Standard assay”, such as can be found in US 7,678,801 and others.

One way to compare the pIC₅₀ and the IC₅₀ from these assays is shown in the table below (such data is also taught, for instance, in US 7,678,801):

TABLE 1

pIC ₅₀	IC ₅₀ (nM)	IC ₅₀ (uM)
4.00	100,000.0	100
5.00	100,000.0	10
6.00	1,000.0	1
7.00	100.0	0.1
8.00	10.0	0.01
9.00	1.0	0.001
10.00	0.1	0.0001

The skilled artisan would readily recognize that this assay teaches a level of binding affinity for the enzyme and that one would be able to determine whether a compound was sufficiently active (as an antagonist) in the assay to be of use clinically. This is not a new assay, it is a standard screening assay in the industry as can readily be seen be the papers submitted in Applicants IDS and in the many filed patent applications by Applicants and others in this field.

While the present application does not have a Detailed Background of the Invention section, this does not detract from the many prior applications of Applicants and other in this field, all of which form the State of the Art. Applicants have submitted in their IDS and 1449 Forms a significant number of papers which demonstrate linkage of p38 kinase inhibition to various disease states.

Prior to the filing of this application, the signaling pathway of p38 kinase had been extensively studied. It was well established in the art that there is a correlation of p38 inhibition and its affect on the pro-inflammatory cytokine cascade. Consequently, Applicants believe that they have provided sufficient grounds of enablement for the compounds of Formula (I) as described herein.

In addressing the Examiner's concern that this is simply an assertion by Counsel, Applicants previously submitted an article on signaling cascades in inflammatory diseases (see Herlaar, E. et al., *Molecular Med Today* (1999), Vol. 5, 439-447). This article and other previously submitted articles on p38 kinase **inhibitors** detail the linkage to a number of acute and chronic inflammatory diseases, such as RA, osteoarthritis, inflammatory bowel disease, toxic shock syndrome, septic shock, asthma, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), and osteoporosis. The skilled artisan would also be aware of the many more articles and work in the field which describes the role of pro-inflammatory cytokines in the diseases enumerated herein.

Applicants respectfully submit that the originally filed disclosure provides sufficient information on how to formulate, how to dose, and how to administer the compounds of Formula (I). For information on how to "use", see pages 22, lines 1 to 42 – page 32, lines 1 -11. As noted the Specification teaches on pages 107, lines 35 to 41 – pages 110, lines 1 – 23 suitable assays to determine biological activity. Based on this, Applicants maintain that the specification is sufficiently enabled and would not require undue experimentation to practice the invention.

However, future assertions of the evidence of this being an art recognized area, one can turn to the US Governments ClinicalTrials.gov database which will retrieve at least 34 studies in this area (although not all were started prior to the filing date of this application). Applicants also submitted another publication (2002) on a structurally unrelated p38 inhibitor which clearly

teaches state of the art and the linkage to inhibition of the p38 MAP kinase (as well as the usage of a similar fluorescent binding assay as Applicants). See Regan et al., J. Med Chem., 45, pg 2994-3008 (2002).

The discovery of p38 (initially termed CSBP, now p38, and the isoforms p38 α and p38 β) provide a mechanism of action for a class of anti-inflammatory compounds for which SK&F 86002 was the prototypic example. These compounds inhibited IL-1 and TNF synthesis in human monocytes at concentrations in the low μ M range [Lee, *et al.*, Int. J. Immunopharmac. 10(7), 835(1988)] and exhibited activity in animal models which are refractory to cyclooxygenase inhibitors [Lee; *et al.*, Annals N. Y. Acad. Sci., **696**, 149(1993)].

The mechanism by which stress signals (including bacterial and viral infection, pro-inflammatory cytokines, oxidants, UV light and osmotic stress) activate p38 is through activation of kinases upstream from p38 which in turn phosphorylate p38 at threonine 180 and tyrosine 182 resulting in p38 activation. MAPKAP kinase-2 and MAPKAP kinase-3 have been identified as downstream substrates of CSBP/p38 which in turn phosphorylate heat shock protein Hsp27 and other substrates. Additional downstream substrates known to be phosphorylated by p38 include kinases (Mnk1/2, MSK1/2 and PRAK) and transcription factors (CHOP, MEF2, ATF2 and CREB).

In addition to inhibiting IL-1 and TNF upregulation in response to inflammatory stimuli, early tool p38 kinase inhibitors (e.g., SK&F 86002 and SB-203580) have been shown to be effective in a number of different cell types in decreasing the synthesis of a wide variety of pro-inflammatory proteins including, IL-6, IL-8, GM-CSF, RANTES and COX-2. Inhibitors of p38 kinase have also been shown to suppress the TNF-induced expression of VCAM-1 on endothelial cells, the TNF-induced phosphorylation and activation of cytosolic PLA2 and the IL-1-stimulated synthesis of collagenase and stromelysin. These and additional data demonstrate that p38 is involved not only cytokine synthesis in response to stress, but also in propagating the consequent cytokine signaling [CSBP/P38 kinase reviewed in Cohen, P. Trends Cell Biol., 353-361(1997)].

Thus, there are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include rheumatoid arthritis, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, gout, traumatic arthritis, rubella arthritis, and acute synovitis.

Inflammatory diseases are also marked by increases in IL-6 and C-reactive protein (CRP), both of which are sensitive to inhibition by p38 inhibitors. IL-6 stimulation of CRP production is directly inhibited by p38 inhibitors in human vascular endothelial cells, and CRP is produced by hepatocytes in response to IL-6. CRP is considered a major risk factor for cardiovascular disease [Circulation 2003.107: 363-369] and may be a significant independent risk factor for chronic obstructive pulmonary disease [Circulation 2003. 107:1514-1519]. IL-6 is also upregulated in endometriosis [Bedaiwy et al., 2002, Human Reproduction 17:426-431; Witz, 2000, Fertility and Sterility 73: 212-214].

In addition to the involvement of p38 signaling in the production of IL-1, TNF, IL-8, IL-6, GM-CSF, COX-2, collagenase and stromelysin, signal transduction via CSBP/p38 is required for the effector functions of several of these same pro-inflammatory proteins plus many others. For example, growth factors such as VEGF, PDGF, NGF signal through surface receptors which in turn activate cellular signaling pathways including p38 MAPK [Ono, K. and Han, J., Cellular Signalling, **12** 1-13 (2000); Kyriakis, JM and Avruch, J. Physiol Rev **81**: 807-869 (2001)]. TGF χ , a key molecule in the control of inflammatory response, also activates p38 as a consequence of engagement of the TGF β receptor. The involvement of CSBP/p38 in multiple stress-induced signal transduction pathways provides additional rationale for the potential utility of CSBP/p38 in the treatment of diseases resulting from the excessive and destructive activation of the immune system, or chronic inflammation. This expectation is supported by the potent and diverse activities described for CSBP/p38 kinase inhibitors [Badger, *et al.*, J. Pharm. Exp. Thera. **279** (3): 1453-1461,

(1996); Griswold, *et al*, Pharmacol. Comm. **7**, 323-229 (1996); Jackson, *et al.*, J. Pharmacol. Exp. Ther. **284**, 687- 692 (1998); Underwood, *et al.*, J. Pharmacol. Exp. Ther. **293**, 281- 288 (2000); Badger, *et al.*, Arthritis Rheum. **43**, 175 -183 (2000)].

Chronic inflammation is also characterized by ongoing remodeling and repair of affected tissue, leading in some cases to excess fibrotic tissue. A role for p38 MAPK in fibrosis is supported by findings that this enzyme mediates signaling of transforming growth factor beta (TGF- β) on markers and proteins of fibrosis. For example, it has been shown that TGF- β increases the kinase activity of p38 MAPK through the TGF- β activated kinase TAK-1 (Hanafusa et al., 1999, J. Biol. Chem. **274**:27161-27167). Furthermore, the p38 inhibitor SB-242235 inhibited the TGF- β -induced increases in fibronectin and thrombospondin (Laping et al., 2002, Molec. Pharmacol. **62**:58-64). These results show that p38 MAPK is a key signaling intermediate for the effect of the pro-fibrotic cytokine TGF- β on components of the extracellular matrix and markers of fibrosis.

P38 also plays a role in directing survival and apoptosis of cells in response to various stimuli. Both survival and apoptosis can be p38 regulated depending on the stimulus and the cell type [Morin and Huot, Cancer Research. **64**:1893-1898 (2004)]. For example, TGF-beta can stimulate apoptosis in murine hepatocytes through activation of gadd45b, a protein involved in cell-cycle control, in a p38 mediated process [Yoo et al, J. Biol. Chem. **278**:43001-43007, (2003)]. In a different response pathway, UV-stress can activate p38 and trigger apoptosis of a damaged cell. P38 has also been shown to promote survival of lymphocytes in response to stress, including neutrophils and CD8+ T cells.

Lastly, CSBP inhibitors have been tested in a number of animal models for anti-inflammatory activity. Model systems were chosen that were relatively insensitive to cyclooxygenase inhibitors in order to reveal the unique activities of cytokine suppressive agents. The inhibitors exhibited significant activity in many such in vivo studies. Most notable are its effectiveness in the collagen-induced arthritis model and inhibition of TNF production in the endotoxic shock model. In the latter study, the reduction in plasma level of TNF correlated with survival and protection

from endotoxic shock related mortality. Also of great importance are the compounds effectiveness in inhibiting bone resorption in a rat fetal long bone organ culture system. See for instance, Griswold et al., (1988) *Arthritis Rheum.* **31**:1406-1412; Badger, et al., (1989) *Circ. Shock* **27**, 51-61; Votta et al., (1994) *in vitro. Bone* **15**, 533-538; Lee et al., (1993). *B Ann. N. Y. Acad. Sci.* **696**, 149-170.

The Herlaar et al. publication (previously submitted) discusses the state of the art in 1999 and describes the role of p38 in the generation of inflammatory mediators and migration of inflammatory cells. This reference demonstrates the role of p38 in many of the functions that are emerging as key to the treatment of a large number of diseases containing an inflammatory component. Herlaar et al. summarizes experimentation with a tool compound, SB 203580 as an inhibitor of the p38 kinase, providing proof that inhibition of this pathway has consequences in cell signaling.

In *In re DiLeone et al.*, 168 USPQ 592 (CCPA 1971), the principal is cited for what is needed to meet the description requirements as it varies depending upon the nature of the invention claimed. The present application, as in the case before the board, contains a specification that clearly describes the terms used therein and also contains many representative examples illustrating the breadth of the claim language. Thus, Applicants believe that they have satisfied that aspect of section §112. Further, Applicants have described and demonstrated that the compounds, as claimed herein, have the disclosed activity of p38 inhibition.

There is no requirement that *in vitro* or *in vivo* data be submitted to substantiate Applicants claimed utility that of inhibition of a cytokine mediated disease state, or inflammation. However, as noted above the specification does provide *in vitro* biological data.

The USPTO has allowed a large number patents which contain either claims to inhibition of the p38 kinase in the following patents, assigned to GSK or an affiliate, or contain in their specification similar biological assays to that described herein. It should be noted that this

list is not inclusive, and merely representative of p38 kinase inhibitors previously allowed by the USPTO:

US Patents 7,208,629; 7,384,963; 7,183,297; 7,432,289; 7,166,623; 7,166,597; 7,396,843; 7,151,118; 7,309,800; 7,626,055; 7,271,289; 7,572,790; 7,425,555; 7,642,276; 7,514,456; 7,709,506; 7,125,898; and 7,687,532.

US 5,658,903; US 5,739,143 ('143); US 6,329,526 ('526); US 6,251,914; US 5,929,076 ('076); US 5,756,499 ('499); US 5,977,103; US 5,864,036 ('036); US 6,046,208; US 5,71,955 ('955); US 6,096,748; US 6,528,512; US 6,599,910; US 6,548,503; US 6,469,018; and US 6,759,410 ('410) all contain claims directed to treating a CSBP/p38 Kinase mediated disease. US Patent '143, '526, '036, '076 & '955 also claims directed to the treatment of inflammation. US Patent '036 & '955 also contain claims directed to inhibition of the synthesis prostaglandin endoperoxide synthase-2.

US 6,774,127 contains claims directed to treating the inflammatory component of a CSBP/p38 Kinase mediated disease. US 6,610,695; and US 6,362,193 contain claims directed to the treatment or prophylaxis of a CSBP/p38 Kinase mediated disease. US 5,686,455 has claims directed to the therapeutic or prophylactic treatment of a cytokine mediated disease state.

US Patents 5,916,891; US 5,593,991; US 5,593,992; US 5,670,527 ('527); US 6,288,062; and US 5,756,499 ('499) all have claims directed to treatment of a cytokine mediated disease; and the '527 & '499 patent also have claims directed to the treatment of inflammation. The '499 patent further contains claims directed to inhibition of the synthesis prostaglandin endoperoxide synthase-2.

Given all of the above which forms the State of the Art, the skilled artisan would not only understand the value of a p38 kinase inhibitor, but the means of determining whether a compound could inhibit the kinase. Inhibition of the p38 kinase has been known to be linked to

more than one credible utility. Consequently, Applicants assert that the Examiner has erred in rejecting the claims as nonenabling under the provisions of 35 U.S.C. §112, first paragraph.

Applicants request reversal of the outstanding rejection for the reasons set forth herein.

CONCLUSION

For the reasons given above, we submit that the Examiner has improperly rejected claims 3, 5-7, 18 and 20 and respectfully request reversal of the rejections.

Respectfully submitted



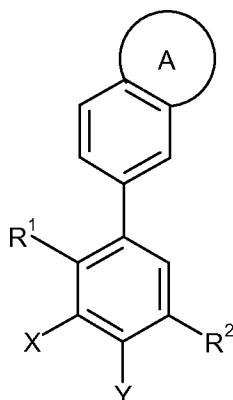
By: _____

Dara L. Dinner
Attorney for Applicants
Registration No. 33,680

GLAXOSMITHKLINE
Corporate Intellectual Property UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939
Phone (610) 270-5017
Facsimile (610) 270-5090

VIII. Claims Appendix

1. (Previously Presented) A compound of formula (I):



(I)

wherein

A is a fused 5-membered heteroaryl ring substituted by $-(CH_2)_m$ aryl or $-(CH_2)_m$ heteroaryl wherein the aryl or heteroaryl is optionally substituted by one or more substituents independently selected from oxo, C₁₋₆alkyl, halogen, -CN, trifluoromethyl, -OR³, $-(CH_2)_nCO_2R^3$, -NR³R⁴, $-(CH_2)_nCONR^3R^4$, -NHCOR³, -SO₂NR³R⁴, -NHSO₂R³ and -S(O)_pR³, and

A is optionally further substituted by one substituent selected from -OR⁵, halogen, trifluoromethyl, -CN, -CO₂R⁵ and C₁₋₆alkyl optionally substituted by hydroxy;

R¹ is selected from methyl and chloro;

R² is selected from -NH-CO-R⁶ and -CO-NH-(CH₂)_q-R⁷;

R³ is selected from hydrogen, $-(CH_2)_r$ -C₃₋₇cycloalkyl, $-(CH_2)_r$ heterocyclyl, $-(CH_2)_r$ aryl, and C₁₋₆alkyl optionally substituted by up to two substituents independently selected from -OR⁸ and -NR⁸R⁹,

R⁴ is selected from hydrogen and C₁₋₆alkyl, or

R³ and R⁴, together with the nitrogen atom to which they are bound, form a 5-or 6-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and N-R¹⁰;

R⁵ is selected from hydrogen and C₁₋₆alkyl;

R⁶ is selected from hydrogen, C₁₋₆alkyl, -(CH₂)_q-C₃₋₇cycloalkyl, trifluoromethyl, -(CH₂)_sheteroaryl optionally substituted by R¹¹ and/or R¹², and -(CH₂)_sphenyl optionally substituted by R¹¹ and/or R¹²;

R⁷ is selected from hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, -CONHR¹³, phenyl optionally substituted by R¹¹ and/or R¹², and heteroaryl optionally substituted by R¹¹ and/or R¹²;

R⁸ and R⁹ are each independently selected from hydrogen and C₁₋₆alkyl;

R¹⁰ is selected from hydrogen and methyl;

R¹¹ is selected from C₁₋₆alkyl, C₁₋₆alkoxy, -(CH₂)_q-C₃₋₇cycloalkyl, -CONR¹³R¹⁴, -NHCOR¹⁴, halogen, -CN, -(CH₂)_tNR¹⁵R¹⁶, trifluoromethyl, phenyl optionally substituted by one or more R¹² groups, and heteroaryl optionally substituted by one or more R¹² groups;

R¹² is selected from C₁₋₆alkyl, C₁₋₆alkoxy, halogen, trifluoromethyl, and -(CH₂)_tNR¹⁵R¹⁶;

R¹³ and R¹⁴ are each independently selected from hydrogen and C₁₋₆alkyl, or

R¹³ and R¹⁴, together with the nitrogen atom to which they are bound, form a 5- or 6-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and N-R¹⁰, wherein the ring may be substituted by up to two C₁₋₆alkyl groups;

R¹⁵ is selected from hydrogen, C₁₋₆alkyl and -(CH₂)_q-C₃₋₇cycloalkyl optionally substituted by C₁₋₆alkyl,

R¹⁶ is selected from hydrogen and C₁₋₆alkyl, or

R¹⁵ and R¹⁶, together with the nitrogen atom to which they are bound, form a 5- or 6-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and N-R¹⁰;

X and Y are each independently selected from hydrogen, methyl and halogen;

m, n, p and q are each independently selected from 0, 1 and 2;

r and s are each independently selected from 0 and 1; and

t is selected from 0, 1, 2 and 3;

with the proviso that when A is substituted by $-(CH_2)_m$ heteroaryl and m is 0, the $-(CH_2)_m$ heteroaryl group is not a 5-membered heteroaryl ring optionally substituted by C_{1-2} alkyl;
or a pharmaceutically acceptable salt thereof.

2. (Previously Presented) A compound according to claim 1 wherein A is a fused 5-membered heteroaryl ring containing up to two heteroatoms independently selected from oxygen and nitrogen.

3. (Previously Presented) A compound according to claim 1 wherein R^1 is methyl.

4. (Previously Presented) A compound according to claim 1 wherein R^2 is $-CO-NH-(CH_2)_q-R^7$.

5. (Previously Presented) A compound according to claim 1 wherein A is substituted by $-(CH_2)_m$ heteroaryl wherein the heteroaryl is a 5- or 6-membered heteroaryl ring containing up to two heteroatoms independently selected from oxygen and nitrogen.

6. (Previously Presented) A compound according to claim 5 wherein the heteroaryl is optionally substituted by one or two substituents independently selected from oxo, C_{1-6} alkyl, halogen, $-OR^3$, $-NR^3R^4$ and $-(CH_2)_nCONR^3R^4$.

7. (Previously Presented) A compound according to claim 6 wherein the heteroaryl is substituted by one or two substituents independently selected from oxo and C_{1-6} alkyl.

8. (Previously Presented) A compound according to claim 1 wherein A is substituted by $-(CH_2)_m$ aryl wherein the aryl is phenyl.

9. (Previously Presented) A compound according to claim 8 wherein the aryl is substituted by one or two substituents independently selected from C₁₋₆alkyl, halogen, -CN, trifluoromethyl, -OR³, -NR³R⁴, -(CH₂)_nCONR³R⁴ and -S(O)_pR³.

10. (Previously Presented) A compound according to claim 1 wherein X is hydrogen or fluorine.

11. ((Previously Presented)) A compound according to claim 1 substantially as hereinbefore defined with reference to any one of Examples 1 to 82, or a pharmaceutically acceptable salt thereof.

12. ((Previously Presented)) A compound selected from:

N-cyclopropyl-3-fluoro-4-methyl-5-(1-phenyl-1*H*-indazol-5-yl)benzamide;

N-cyclopropyl-3-fluoro-5-[1-(4-fluorophenyl)-1*H*-indazol-5-yl]-4-methylbenzamide;

N-cyclopropyl-3-fluoro-5-[1-(4-fluoro-2-methylphenyl)-1*H*-indazol-5-yl]-4-methylbenzamide;

N-cyclopropyl-3-fluoro-4-methyl-5-{1-[4-(4-morpholinyl)phenyl]-1*H*-indazol-5-yl}benzamide;

N-ethyl-3-fluoro-4-methyl-5-(1-phenyl-1*H*-indazol-5-yl)benzamide;

N-(cyclopropylmethyl)-3-fluoro-4-methyl-5-(1-phenyl-1*H*-indazol-5-yl)benzamide;

N-cyclopropyl-3-fluoro-4-methyl-5-{1-[4-(methylsulfonyl)phenyl]-1*H*-indazol-5-yl}benzamide;

N-cyclopropyl-3-fluoro-4-methyl-5-(1-{4-[2-(methylamino)-2-oxoethyl]phenyl}-1*H*-indazol-5-yl)benzamide;

N-cyclopropyl-3-[1-(4-{[2-(dimethylamino)ethyl]amino}phenyl)-1*H*-indazol-5-yl]-5-fluoro-4-methylbenzamide;

N-cyclopropyl-3-fluoro-4-methyl-5-{1-[4-(tetrahydro-2*H*-pyran-4-ylamino)phenyl]-1*H*-indazol-5-yl}benzamide;

N-cyclopropyl-3-fluoro-4-methyl-5-(1-{4-[(tetrahydro-2-furanylmethyl)amino]phenyl}-1*H*-indazol-5-yl)benzamide;

N-cyclopropyl-3-(1-{4-[(2,3-dihydroxypropyl)amino]phenyl}-1*H*-indazol-5-yl)-5-fluoro-4-methylbenzamide;

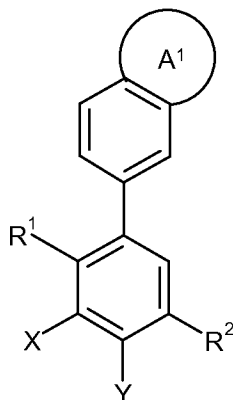
N-cyclopropyl-3-fluoro-4-methyl-5-{1-[(1-oxido-2-pyridinyl)methyl]-1*H*-indazol-5-yl}benzamide;
N-ethyl-3-[3-(4-fluorophenyl)-1*H*-indazol-6-yl]-4-methylbenzamide;
N-cyclopropyl-3-[3-(4-fluorophenyl)-1*H*-indazol-6-yl]-4-methylbenzamide;
N-ethyl-4-methyl-3-{3-[4-(methyloxy)phenyl]-1*H*-indazol-6-yl}benzamide;
N-cyclopropyl-4-methyl-3-{3-[4-(methyloxy)phenyl]-1*H*-indazol-6-yl}benzamide;
N-(1-ethyl-1*H*-pyrazol-5-yl)-3-fluoro-5-[3-(4-fluorophenyl)-1*H*-indazol-6-yl]-4-methylbenzamide;
N-ethyl-3-fluoro-5-{3-[4-fluoro-2-(methyloxy)phenyl]-1*H*-indazol-6-yl}-4-methylbenzamide;
N-(1,4-dimethyl-1*H*-pyrazol-5-yl)-3-fluoro-5-[3-(4-fluorophenyl)-1*H*-indazol-6-yl]-4-methylbenzamide; [[and]]
N-(1,4-dimethyl-1*H*-pyrazol-5-yl)-3-[3-(4-fluorophenyl)-1*H*-indazol-6-yl]-4-methylbenzamide;
or a pharmaceutically acceptable salt thereof.

13. ((Previously Presented)) A pharmaceutical composition comprising at least one compound according to claim 1, or a pharmaceutically acceptable salt thereof, in association with one or more pharmaceutically acceptable excipients, diluents and/or carriers.

14. -17. (Cancelled)

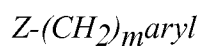
18. ((Previously Presented)/withdrawn) A process for preparing a compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, which comprises :

(a) reacting a compound of formula (II) :

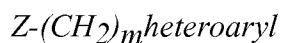


(II)

in which R^1 , R^2 , X and Y are as defined in claim 1 and A^1 is an unsubstituted fused 5-membered heteroaryl ring with a halide derivative of formula (IIIA) or (IIIB) :



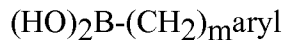
(IIIA)



(IIIB)

in which $-(CH_2)_m^{aryl}$ and $-(CH_2)_m^{heteroaryl}$ are as defined in claim 1 and Z is halogen, in presence of a base,

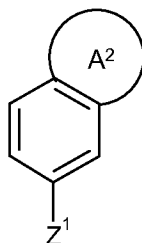
or, when A is substituted by $-(CH_2)_m^{aryl}$ wherein m is 0, reacting the compound of formula (II) with a boronic acid compound of formula (IV)



(IV)

in which $-(CH_2)_m^{aryl}$ is as defined in claim 1;

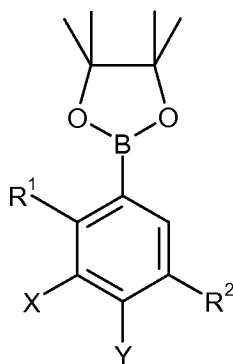
(b) reacting a compound of formula (V):



(V)

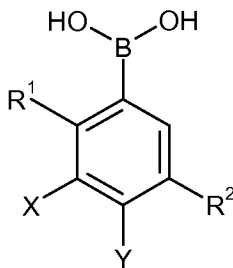
in which A^2 is A as defined in claim 1 and Z^1 is halogen,

with a compound of formula (VIA) or (VIB) :



(VIA)

or

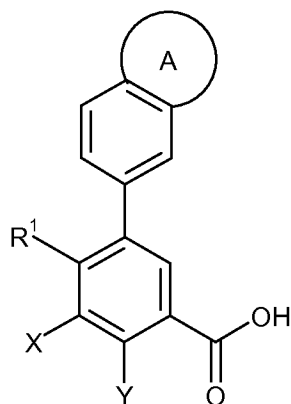


(VIB)

in which R^1 , R^2 , X and Y are as defined in claim 1,

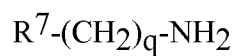
in presence of a catalyst;

(c) reacting a compound of formula (XVI) :



(XVI)

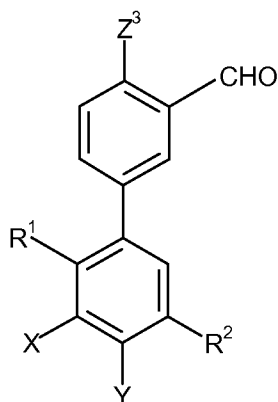
in which A, R¹, X and Y are as defined in claim 1,
 with an amine compound of formula (XV) :



(XV)

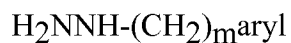
in which R⁷ and q are as defined in claim 1,
 under amide forming conditions;

d) when A is a fused pyrazolyl, reacting a compound of formula (XVII) :



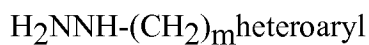
(XVII)

in which R¹, R², X and Y are as defined in claim 1 and Z³ is halogen,
 with a hydrazine derivative of formula (VIII A) or (VIII B) :



(VIII A)

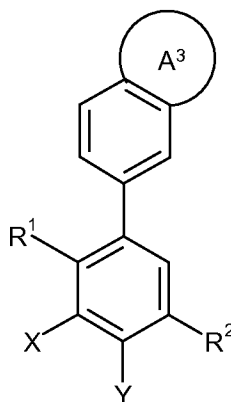
or



(VIII B)

in which $-(\text{CH}_2)_m\text{aryl}$ and $-(\text{CH}_2)_m\text{heteroaryl}$ are as defined in claim 1;

(e) reacting a compound of formula (XVIII) :



(XVIII)

in which R¹, R², X and Y are as defined in claim 1 and A³ is a fused 5-membered heteroaryl ring substituted by halogen, with a suitable boronic acid derivative; or

(f) final stage modification of one compound of formula (I) as defined in claim 1 to give another compound of formula (I) as defined in claim 1.

19 (Previously Presented). A compound according to claim 2 wherein R¹ is methyl.

20. (Previously Presented) A compound according to claim 2 wherein R² is $-\text{CO}-\text{NH}-(\text{CH}_2)_q-\text{R}^7$.

21. (Previously Presented) A compound according to claim 19 wherein R² is -CO-NH-(CH₂)_q-R⁷.

22. ((Previously Presented)) A pharmaceutical composition comprising at least one compound according to claim 12, or a pharmaceutically acceptable salt thereof, in association with one or more pharmaceutically acceptable excipients, diluents and/or carriers.

23. (Withdrawn) The compound according to Claim 1 which is:

N-cyclopropyl-3-fluoro-4-methyl-5-{3-[4-(methyloxy)phenyl]-1,2-benzisoxazol-6-yl}benzamide;

N-cyclopropyl-3-fluoro-5-[3-(4-hydroxyphenyl)-1,2-benzisoxazol-6-yl]-4-methylbenzamide; or
3-fluoro-5-[3-(4-fluorophenyl)-1H-indazol-6-yl]-4-methyl-N-(1-methyl-1H-pyrazol-5-yl)benzamide; or a pharmaceutically acceptable salt thereof.

X. Related Proceedings Appendix

None.

